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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,994	07/02/2002	Frank Luyten	50304/029001	5817

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,994	LUYTEN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-59,61,63 and 64* is/are pending in the application.

4a) Of the above claim(s) *31-42 and 46-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-45, 61, 63 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/6/07 has been entered.

Applicants' Amendment, filed 8/6/07, has been entered. Claims 1-30, 62 are cancelled; claims 31-59, 61, 63, 64 are pending; claims 31-42 and 46-59 are withdrawn; claims 43-45, 61, 63 and 64 are under current examination

The Luyten Declaration, filed 8/6/07, has been considered.

Election/Restrictions

Claims 31-42 and 46-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/4/05.

Applicant's election without traverse of Group XII (claims 43-45, 60 and 61) in the reply filed on 8/4/05 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-45, 61, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A purified culture of differentiated precursor human cells isolated from periosteum, bone marrow or synovial membrane, that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue, wherein the cells express CDMP-1.

The specification does not reasonably provide enablement for the breadth of the claims, which encompass cells from any animal source, wherein the cells express CDMP-1 and are isolated from periosteum, bone marrow, or synovial membrane from any animal, and have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue; and therapeutic compositions comprising said differentiated precursor cells; implants comprising said cells.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The scope of enablement has been determined to only be pertinent to human cells. The working examples (see p. 23) in the specification are only directed to isolating the claimed cells from human sources. The state of the art (Luyten et al, cited previously) teach that the mouse homologue of CDMP-1 is Gdf5. Although they teach that this gene is involved in chondrogenesis *in vitro*, and osteogeneisis *in vitro* and *in vivo*, there is no indication of the specific cells, isolated from a mouse, that would express CDMP-1 and have the characteristics required by the claims. There is no specific teaching for the breadth of other animal sources, such as birds, or any other mammals other than human cells, which express CDMP-1 and have

the specific phenotypes claimed. Accordingly, the claimed cells have been limited to human cells.

Response to Arguments. The amendment to the claims overcomes the prior rejection, with specific regard to the deletion of recitation of markers that are co-expressed and/or co-detectable with CDMP-1.

Applicants' Arguments.

Negative Marker. Applicants argue that the reasoning with regard to the negative markers characterizing the precursor cells is inappropriate. In particular, whether or not the "mature phenotype" is the present application clearly states that the precursor cells of the present invention can be identified by the expression of a positive marker (*i.e.*, CDMP-1) and the absence of expression of a "negative marker". Thus, the invention does not require the identification of all positive and/or all negative markers potentially associated with the mature chrondrocyte phenotype (see pages 11-12 of the Response).

Additionally, Applicants argue that the Examiner has provided an improper interpretation of claim 61, particularly with regard to the "negative marker". In particular, Applicants argue that because claims 43-45 are directed to cells that are characterized by positive markers (*i.e.*, CDMP-1), Applicants assert that the dependent claim is used to further characterize the invention, and there is no obligation that the further characterizing feature be of the same nature as recited in the independent claim from which it depends. Applicants argue that it is clear that a cell population can be characterized by the expression of one or more markers, and in addition, can be further characterized by the fact that certain negative markers are not expressed. See pages 12-13 of the Response.

Response to Arguments. These arguments have been considered, and are found to be persuasive in view of Applicants' amendments to the claims, which are solely directed to the expression of CDMP-1 in the claimed cells. However, the Examiner notes that the prior rejection is not directed to a requirement that the

further characterizing feature be of the same nature as recited in the independent claim. In fact, the further characterization of the cells requires what is present in the independent claim. Thus, only one cell population is claimed in independent claims 43-45. These cell populations are identified by the expression of CDMP-1. The cells are required to be homogenous. Thus, the absence of negative markers (in any combination), is an inherent property in the homogenous population of cells, expressing CDMP-1.

Applicants' Arguments.

Therapeutic Benefit. Applicants have provided the Luyten Declaration for support that the markers identified using the nude mouse model are reliable markers for the ability of cells to produce stable hyaline cartilage *in vivo*, particularly when injected into a cartilage defect. Applicants state that the identification of markers of chondrocyte phenotypic stability using the nude mouse model has been useful for studying chondrocyte phenotypic stability, and that the expression of these markers by a chondrocyte cell population was found to correlate with the ability of a population to restore a chondrocyte defect. Thus, Applicants argue that this data demonstrates the expression of markers identified by the nude mouse model as a reliable indicator of *in vivo* therapeutic effectiveness of a cell population. See pages 13-14. Applicants further argue that the cell cultures of the claimed invention were implanted in mice and then analyzed for cellular composition, and found that the injected precursor cells had indeed differentiated into chondrocytes *in vivo.* Applicants point to Table 2 and Example 7 of the specification.

Response to Arguments. Applicants' arguments and the Luyten Declaration have been fully considered but are not persuasive. The Luyten Declaration states that markers for "the ability of cells to produce stable hyaline cartilage *in vivo* were identified using the nude mouse model described in the specification." See Annex (p. 3, #1 of the Declaration). This statement is unclear as to if the cells that are

identified are the same cells as those instantly claimed. Although the Declaration teaches cell population "expressing markers" for cartilage forming ability (see page 2, #5 of the Declaration), it is unclear from this statement as to whether the expressed marker is CDMP-1. There is no specific indication that cells that were used in the experiment discussed in the Declaration expressed CDMP-1, and were isolated from periosteum, bone marrow or synovial membrane. The Luyten Declaration, p. 2, #5 states that the cells were obtained from "a biopsy". The only biopsy that is discussed in the annex section is that from cartilage biopsies, not a biopsy from periosteum, bone marrow or synovial membrane. There is no indication that the "markers" that are not specifically identified in the Declaration include CDMP-1.

The Luyten Declaration is not persuasive for the following reasons:

1. The Declaration does not specifically show that the cells used are the exact same cells as those instantly claimed.

2. The Declaration does not show using the exact same cells, as those instantly claimed, in a nude mouse model, and then using those cells for implantation.

3. The Declaration does not provide guidance to show that source of the cells is the same as what is instantly claimed (*i.e.*, periostuem, bone marrow or synovial membrane).

4. The Declaration does not specifically state the markers that are identified which are "representative of the ability of the cells to produce stable hyaline cartilage when injected *in vivo*" (p. 1, # 4 of the Declaration). There is no indication that the cells specifically express CDMP-1.

5. The Declaration does not specifically show that the cells are a homogenous culture, as required by the claims. The Declaration states that that the cell population is obtained from a biopsy, and expresses "markers" which are identified to be representative of cartilage formation, but there is no indication that

the cells are purified and homogenous. For example, the Annex, #2, states that the cell populations were "assessed for the expression of relevant markers by molecular screening... The cells were then further cultured before being re-implanted into the cartilage defect in the patient." There is no indication of purification, or that the resultant cell population is homogenous prior to re-implantation.

Accordingly, Applicants' arguments and the Luyten Declaration, with regard to utilizing the cells for therapeutic purposes, are not found to be persuasive. Applicants' point to Example 7 and Table 2 of the specification for support to show that cell cultures of the instant invention differentiated into chondrocytes *in vivo*. It is reiterated that the working examples fail to correlate to a therapeutic result in utilizing the claimed cells, as they are directed to injection of immunodeficient, nude mice, which would not be considered a model for an immunocompetent individual. The working example shows *in vivo* implantation of the cells by intramuscular injection of the cells into nude mice. This is not analogous to what would be considered a therapeutic treatment. For example, the specification contemplates the instant invention in the context of a mammal with cartilage defects (see page 22, lines 23-35, for example). The nude mouse, as taught in the working example, is not considered a model of cartilage defect. The Luyten Declaration fails to overcome the prior rejection of record for the reasons listed above.

Accordingly, it is maintained that the specification fails to provide specific teachings or guidance for the expression of CDMP-1 in cells, other than human cells, which would function as the claimed cells, when isolated form the same tissues, the lack of teachings or guidance to overcome the unpredictability in the art with regard to the intended use of the therapeutic compositions/implants for therapeutic purposes, the lack of nexus between the *in vivo* example, utilizing a nude, immunodeficient mouse and any resultant therapeutic effect, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Written Description

The prior rejection of claims 43-45, 61 and 63-64 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendments to the claims which no longer recite markers that are "co-expressed and/or co-detectable with CDMP-1". Additionally, the rejection of claim 64, for lacking written description, is withdrawn in view of Applicants' amendment to the claim, which no longer recites, "another marker of the mature chondrocyte phenotype."

Claim Rejections - 35 USC § 112

The prior rejection of claims 43, 45 and 64 is withdrawn in view of Applicants' amendment to the claims, which now recites "homogenous".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45, 61 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is indefinite. The claim recites an implant, which is "optionally suitable for connective tissue implantation." It is unclear what else an implant would be used for, other than implantation. Appropriate correction or clarification is required.

The metes and bounds of claims 61 and 64 are unclear, with regard to the phrase, "the absence of a negative marker". In particular, a negative marker is one that is not expressed; therefore the absence of something that is not expressed (*i.e.,*

a double negative) would appear to be expressed. This renders the claims indefinite. If Applicants intend for this language to mean that a specific marker is not expressed, it is suggested that the claim be amended to reflect this.

Claim Rejections - 35 USC § 102

The following rejections are withdrawn in view of Applicants' amendments to the claims, which now require a homogenous population of precursor cells:

1. The rejection of claims 43-44, 61 and 64 under 35 U.S.C. 102(b) as being anticipated by Takahashi *et al.*

2. The rejection of claims 43-45, 61, 63 and 64 under 35 U.S.C. 102(b) as being anticipated by Erlacher *et al.*

3. The rejection of claims 43-45, 61, 63 and 64 under 35 U.S.C. 102(b) as being anticipated by Chang *et al.*

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Thaian N. Ton/
Primary Examiner
Art Unit 1632